

A4

of at least one compound chosen from the compounds of the formula I as claimed in claim 1 and their physiologically tolerable salts.

A5

12. (NEW) A method of treating cardiovascular disorders, thromboembolic diseases or restenoses, comprising administering to a patient an effective amount of at least one compound chosen from the compounds of the formula I as claimed in claim 1 and their physiologically tolerable salts.

### REMARKS

#### **Status of the Claims**

Claims 1-11 were originally filed in this application. Claims 1 and 7 are amended solely to correct the format of superscripted and subscripted terms such as "R<sup>20</sup>" and "(C<sub>1</sub>-C<sub>4</sub>)," and to correct an error in the indentation of the line beginning "Het is" in claim 1. Paragraph 015 of the specification is amended to correct similar typographical errors. Claim 11 is amended and claim 12 is added in order to split the method originally recited in claim 11 into two separate claims. Because these amendments only alter the format of the claims and correct typographical errors, they do not introduce new matter, require a new search of the art, or change the scope of the claims. Applicants respectfully request entry of these amendments.

#### **Rejection of claims 1-11 under 35 U.S.C. § 103(a)**

The Office rejected claims 1-11 as allegedly obvious over U.S. Patent No. 5,703,050, to Klingler et al. (Klingler) and U.S. Patent No. 5,314,902, to Tjoeng et al.

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(Tjoeng). (Office Action at page 2.) The Office contends that one of skill in the art would be motivated to modify the teachings of Klingler and Tjoeng to obtain the instant claimed compounds simply because they are all useful in thrombin inhibition.

Applicants respectfully traverse this rejection.

The Office contends that Klingler teaches "carbamimido-phenylurea derivatives of the type recited in the claims." However, the genus taught in Klingler and the instant claimed genus of compounds do not overlap and contain several important chemical differences. For example, the compounds of Klingler and those of the instant application necessarily differ in the chemical group farthest from the phenyl ring: W in Klingler and R<sup>4</sup> in the instant genus. In Klingler, this group comprises a carbonyl, sulfonic acid, sulfonamide, or tetrazolyl. (Klingler at column 1, lines 38-44.) In the instant genus it may be "(C1-C12)-alkyl, (C6-C14)-aryl, (C6-C14)-aryl-(C1-C4)-alkyl-, Het, and Het-(C1-C4)-alkyl-, wherein the alkyl, aryl, and Het groups are unsubstituted or substituted by at least one identical or different substituent R<sup>10</sup>." (Claim 1.) Tetrazolyl, which contains 4 nitrogen atoms, is not a "Het" group. (See the specification at page 10, lines 20-23, for example.) "R<sup>4</sup> and R<sup>5</sup> together" may also form a "3-membered to 8-membered ring" as described in claim 1. Therefore, there is nothing in Klingler to suggest replacing W with any of the instant R<sup>4</sup> functional groups. There is also nothing in Klingler to suggest halogenating the backbone phenyl group.

The teachings of Tjoeng do not remedy the deficiency of Klingler. The Tjoeng compounds can have a different number of carbon atoms in the chain (where n = 1-3) and contain an ester group at the end of the molecule farthest from the phenyl ring. For example, one of skill in the art would not arrive at the claimed combinations of R<sup>3</sup>, R<sup>4</sup>,

and R<sup>5</sup> groups from combining the disclosures of Klingler and Tjoeng because the functionalities at or near these positions in the compounds of Klingler (carbonyl, sulfonic acid, sulfonamide, tetrazolyl) and Tjoeng (ester) are chemically distinct from those claimed in the instant application and from each other.

In addition, the compounds disclosed in Klingler and Tjoeng are designed as antagonists of integrin receptors, such as the fibrinogen receptor GPIIa/IIIb. (Klingler at col. 14, lines 55-65; Tjoeng at col. 1, lines 14-25; and Specification at page 6, paragraph 009.) In contrast, the compounds of the instant invention are designed to inhibit hydrolysis of substrates by factor VIIa. (Specification at page 6, paragraph 009, and at pages 69-71.) These two target proteins are structurally and functionally unrelated. GPIIa/IIIb is a large membrane-imbedded glycoprotein complex, while factor VIIa is a serine protease. Moreover, neither Klingler nor Tjoeng suggests that thio(urea) derivatives could be useful as factor VIIa inhibitors. Indeed, the observation that two unrelated proteins may both be involved in the same biological pathway is not in itself a sufficient reason to conclude that if one set of thio(urea) derivatives inhibits one of the proteins, that a different set of thio(urea) derivatives can inhibit the other. Yet, at best, this is all that the teachings of Klingler and Tjoeng provide. Thus, the combination of Klingler and Tjoeng does not motivate one of skill in the art to prepare the particular set of compounds of the instant invention, and does not provide any expectation that one of skill in the art could successfully inhibit factor VIIa with the particular claimed compounds.

Finally, the Federal Circuit has repeatedly stated that to make a *prima facie* case of obviousness, "particular findings must be made as to the reason the skilled artisan,

with no knowledge of the claimed invention, would have selected *these components in the manner claimed*" (emphasis added). *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002), quoting *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). The Office has provided no evidence to show that the combination of Klingler and Tjoeng would lead one of skill in the art to the present claimed compounds, and thus has failed to meet the substantial evidence standard of *In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Instead, it has merely made a conclusory statement that compounds similar to those of Klingler and Tjoeng would be expected to inhibit thrombin. (Office Action at page 2.) The Federal Circuit has recently pointed out that the Office "cannot rely on conclusory statements" in establishing a *prima facie* case of obviousness, "but must set forth the rationale on which it relies," and that "[t]his precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Lee*, 277 F.3d at 1343, 1345, 61 U.S.P.Q.2d at 1433, 1435 (Fed. Cir. 2002) (citations omitted). Because the Office has failed to set forth a rationale for this rejection that meets the substantial evidence standard, Applicants respectfully request that this rejection be withdrawn.

#### **Rejection of claim 11 under 35 U.S.C. § 112**

The Office also rejected claim 11, asserting that methods of treating cardiovascular disorders, thromboembolic diseases, or restenoses are not enabled.

(Office Action at pages 2-3.) Applicants traverse this rejection.

The Office acknowledges that methods of inhibiting factor VIIa are enabled, but contends that the specification "does not give any guidance as to the full range of

conditions which could be treated using the instant claimed process.” However, the observation that the claimed compounds can inhibit factor VIIa, in fact, provides such guidance because factor VIIa initiates and is required for blood coagulation, and because defects in the regulation of blood coagulation cause or aggravate many cardiovascular disorders. (Specification at pages 2-3, paragraph 004; G. Broze, *Blood Coagulation and Fibrinolysis* 6 (Suppl 1):S7, submitted to the Office on June 6, 2001.) For example, overactivity of the blood coagulation cascade may lead to restenoses following balloon angioplasty or near an implanted stent and can cause thromboses or arterial plaque buildup. One of skill in the art is capable of determining which disorders would be benefited by inhibition of the blood coagulation pathway that requires factor VIIa. The specification also provides guidance to cardiovascular conditions treatable by the compounds of the invention at pages 45-46, paragraph 77, for example. The specification also provides guidance as to dosage levels and administration methods at pages 42-47, paragraphs 72-79.

The Office goes on to assert that “[t]he nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities.” While approval by the Food and Drug Administration may require *in vivo* testing, this is not the standard under which enablement for patentability is judged. M.P.E.P. § 2107.03(V). The proper standard is whether one of skill in the art would believe that the *in vitro* data in the specification reasonably correlates with the claimed utility (emphasis added). M.P.E.P.

§§ 2107.03(III) and 2164.02. The Office further contends that there is “no absolute predictability” in the pharmaceutical arts even when there is a high degree of skill in the

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art. However, only reasonable predictability is considered sufficient correlation with the claimed utility (emphasis added). A rigorous or exact correlation is not required.

M.P.E.P. § 2107.03(III); *Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985).

Applicants have provided data in the specification showing that many of the disclosed compounds inhibit factor VIIa with inhibition constants in the low nanomolar range. (Specification at pages 69-71; e.g., compounds 30, 36, 37, 49, 51, 52, 54, 60, 61, and 64.) Other studies have shown that compounds that inhibit factor VIIa *in vitro* can effectively treat cardiovascular disorders, such as restenoses and thromboses *in vivo*. A publication by Harker et al. shows that arterial lesion formation following balloon angioplasty in monkeys was reduced by 50% using a concentration of a factor VIIa inhibitor sufficient to inhibit factor VIIa function *in vitro*. (*Haemostasis* 6 (Suppl 1):76-82 (1996) submitted to the Office on June 6, 2001). A publication by Y. Jang et al. discloses that factor VIIa activity increases three fold in rabbits fed a hypercholesterolemic diet, suggesting a link between high factor VIIa activity and arteriosclerosis. (Y. Jang et al. *Circulation* 92:3041-3050 (1995) submitted to the Office concurrently herewith at page 14). The study also showed that infusion of rabbit arteries with a factor VIIa inhibitor that inhibited factor VIIa activity *in vitro* led to decreased restenosis following balloon angioplasty. (Jang et al. pages 9-13, and 16.) Data provided in Berkner et al. further shows that a compound inhibiting factor VIIa *in vitro* can also reduce blood coagulation, restenosis, and thrombosis in animal models. (WO 96/12800 at pages 41-59 submitted to the Office on June 6, 2001). Similar data are presented in Petersen et al. (WO 97/47651 submitted to the Office on June 6, 2001.)

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These studies show that there is an art-recognized correlation between factor VIIa inhibition *in vitro* and effective treatment of cardiovascular disorders *in vivo*. These studies also demonstrate that one of skill in the art is capable of determining an appropriate concentration of inhibitor from *in vitro* data that will be useful in reducing vascular lesion formation, thromboses, and restenoses in animal subjects, including primates. Finally, the citations above show that the techniques used to treat subjects with factor VIIa inhibitors are known in the art and that there are a number of available animal models. Thus, Applicants submit that the state of the art and the level of skill are such that *in vitro* inhibition of factor VIIa is sufficient to correlate to treatment of such conditions *in vivo*. Therefore, Applicants request the withdrawal of this rejection.

#### CONCLUSION

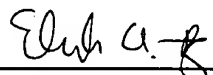
In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of claims 1-12.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

Dated: June 27, 2002

By:   
Elizabeth A. Doherty  
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## APPENDIX TO AMENDMENT OF JUNE 27, 2002

### Amendments to the Specification

Please replace paragraph number 015 with the following:

[015] Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like [(C1-C8)- alkyl] (C<sub>1</sub>-C<sub>8</sub>)-alkyl is to be understood as comprising, among others, saturated acyclic [(C1-C8)-] (C<sub>1</sub>-C<sub>8</sub>)-alkyl, [(C3-C8)-] (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, cycloalkyl-alkyl- groups like [(C3-C7)-cycloalkyl-(C1-C3)-alkyl-] (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>3</sub>)-alkyl- wherein the total number of carbon atoms can range from 4 to 8, and unsaturated [(C2-C8)-alkyl] (C<sub>2</sub>-C<sub>8</sub>)-alkyl like [(C2-C8)-alkenyl or (C2-C8)-alkynyl] (C<sub>2</sub>-C<sub>8</sub>)-alkenyl or (C<sub>2</sub>-C<sub>8</sub>)-alkynyl. Similarly, a group like [(C1-C4)-alkyl] (C<sub>1</sub>-C<sub>4</sub>)-alkyl is to be understood as comprising, among others, saturated acyclic [(C1-C4)-alkyl] (C<sub>1</sub>-C<sub>4</sub>)-alkyl, [(C3-C4)-cycloalkyl] (C<sub>3</sub>-C<sub>4</sub>)-cycloalkyl, cyclopropyl-methyl- and unsaturated [(C2-C4)-alkyl] (C<sub>2</sub>-C<sub>4</sub>)-alkyl like [(C2-C4)-alkenyl or (C2-C4)-alkynyl] (C<sub>2</sub>-C<sub>4</sub>)-alkenyl or (C<sub>2</sub>-C<sub>4</sub>)-alkynyl.

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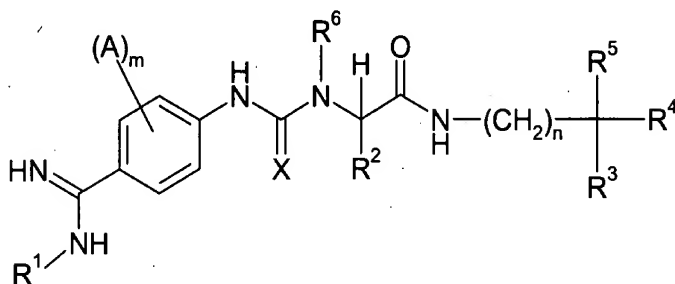
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**Amendments to the Claims**

Please amend claims 1, 7, and 11 as follows:

1. (AMENDED) A compound of the formula I,



wherein

$m$  is 0, 1, 2, 3, or 4;

$n$  is 0, 1, 2, or 3;

$A$  is halogen;

$X$  is sulfur or oxygen;

$\text{R}^1$  is chosen from hydrogen, hydroxy, [(C1-C12)-alkoxycarbonyl-, (C6-C14)-aryl-(C1-C4)-alkoxycarbonyl-, and (C6-C14)-aryloxycarbonyl-] (C<sub>1</sub>-C<sub>12</sub>)-alkoxycarbonyl-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl-, and (C<sub>6</sub>-C<sub>14</sub>)-aryloxycarbonyl-, wherein each of the aryl groups is unsubstituted or substituted by at least one identical or different substituent chosen from

[(C1-C12)-alkyl, halogen and (C1-C12)-alkoxy] (C<sub>1</sub>-C<sub>12</sub>)-alkyl, halogen and (C<sub>1</sub>-C<sub>12</sub>)-alkoxy;

R<sup>2</sup> is chosen from hydrogen, [(C1-C12)-alkyl, (C6-C14)-aryl, (C6-C14)-aryl-(C1-C4)-alkyl-, R20-(C1-C12)-alkyl-, R20-(C6-C14)-aryl-, and R20-(C6-C14)-aryl-(C1-C4)-alkyl-, wherein R20 is chosen from hydroxycarbonyl-, aminocarbonyl-, (C1-C12)-alkoxycarbonyl-, and (C6-C14)-aryl-(C1-C4)-alkoxycarbonyl-] (C<sub>1</sub>-C<sub>12</sub>)-alkyl, (C<sub>6</sub>-C<sub>14</sub>)-aryl, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, R<sup>20</sup>-(C<sub>1</sub>-C<sub>12</sub>)-alkyl-, R<sup>20</sup>-(C<sub>6</sub>-C<sub>14</sub>)-aryl-, and R<sup>20</sup>-(C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, wherein R<sup>20</sup> is chosen from hydroxycarbonyl-, aminocarbonyl-, (C<sub>1</sub>-C<sub>12</sub>)-alkoxycarbonyl-, and (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl-;

R<sup>3</sup> is chosen from hydrogen, cyano, hydroxy, and [(C1-C12)-alkyl] (C<sub>1</sub>-C<sub>12</sub>)-alkyl;

R<sup>4</sup> is chosen from [(C1-C12)-alkyl, (C6-C14)-aryl, (C6-C14)-aryl-(C1-C4)-alkyl-, Het, and Het-(C1-C4)-alkyl-] (C<sub>1</sub>-C<sub>12</sub>)-alkyl, (C<sub>6</sub>-C<sub>14</sub>)-aryl, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, Het, and Het-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, wherein the alkyl, aryl and Het groups are unsubstituted or substituted by at least one identical or different substituent [R10] R<sup>10</sup>;

R<sup>5</sup> is chosen from hydrogen, [(C1-C12)-alkyl, (C6-C14)-aryl, (C6-C14)-aryl-(C1-C4)-alkyl-, Het, Het-(C1-C4)-alkyl-, (C6-C14)-aryl-(C1-C4)-alkyl-

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aminocarbonyl-, and Het-(C1-C4)-alkyl-aminocarbonyl-] (C<sub>1</sub>-C<sub>12</sub>)-alkyl-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, Het-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-aminocarbonyl-, and Het-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-aminocarbonyl-, wherein the alkyl, aryl and Het groups are unsubstituted or substituted by at least one identical or different substituent [R<sup>10</sup>] R<sup>10</sup>;

or

R<sup>4</sup> and R<sup>5</sup> together with the carbon atom to which they are bonded form a saturated or unsaturated 3-membered to 8-membered ring which is a carbocyclic ring or a heterocyclic ring containing 1, 2 or 3 identical or different ring heteroatoms chosen from nitrogen, oxygen and sulfur, and which is optionally condensed to one or two saturated or unsaturated carbocyclic ring systems or heterocyclic ring systems containing 5 to 10 ring atoms of which 1, 2 or 3 are identical or different ring heteroatoms chosen from nitrogen, oxygen and sulfur, wherein the resulting R<sup>4</sup>(R<sup>5</sup>)C group is unsubstituted or substituted by at least one identical or different substituent R<sup>10</sup>;

R<sup>6</sup> is chosen from hydrogen, hydroxy, (C<sub>1</sub>-C<sub>8</sub>)-alkoxy, and (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkoxy-;

R<sup>10</sup> is chosen from (C<sub>1</sub>-C<sub>12</sub>)-alkyl, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkoxy, (C<sub>1</sub>-C<sub>4</sub>)-alkoxy-(C<sub>2</sub>-C<sub>4</sub>)-alkoxy-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkoxy-, (C<sub>6</sub>-

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C<sub>14</sub>)-aryloxy-, Het-oxy-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkoxy-, (C<sub>6</sub>-C<sub>14</sub>)-aryl, Het, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, trifluoromethoxy, trifluoromethyl, halogen, oxo, hydroxy, amino, (C<sub>1</sub>-C<sub>12</sub>)-alkylcarbonylamino-, aminocarbonylamino-, (C<sub>6</sub>-C<sub>14</sub>)-arylcarbonylamino-, Het-carbonylamino-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylcarbonylamino-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkylcarbonylamino-, (C<sub>1</sub>-C<sub>8</sub>)-alkylcarbonyl-, (C<sub>6</sub>-C<sub>14</sub>)-arylcarbonyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkylaminocarbonyl-, (C<sub>6</sub>-C<sub>14</sub>)-arylaminocarbonyl-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylaminocarbonyl-, Het-aminocarbonyl-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkylaminocarbonyl-, aminocarbonyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl-, hydroxycarbonyl-, cyano, nitro, amidino, acetimino, tri-((C<sub>1</sub>-C<sub>4</sub>)-alkyl)ammonio-, (C<sub>1</sub>-C<sub>8</sub>)-alkylamino-, di-((C<sub>1</sub>-C<sub>8</sub>)-alkyl)amino-, hydroxycarbonylmethoxy-, (C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl-, (C<sub>6</sub>-C<sub>14</sub>)-arylsulfonyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkylaminosulfonyl-, (C<sub>6</sub>-C<sub>14</sub>)-arylaminosulfonyl-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylaminosulfonyl-, Het-aminosulfonyl-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkylaminosulfonyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonylamino-, (C<sub>6</sub>-C<sub>14</sub>)-arylsulfonylamino-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylsulfonylamino-, Het-sulfonylamino-, and Het-(C<sub>1</sub>-C<sub>4</sub>)-alkylsulfonylamino-, wherein (C<sub>1</sub>-C<sub>12</sub>)-alkylcarbonylamino- representing R<sup>10</sup> is unsubstituted or substituted in the alkyl group by a substituent chosen from amino, hydroxy and (C<sub>1</sub>-C<sub>4</sub>)-alkoxy, and wherein (C<sub>1</sub>-C<sub>12</sub>)-alkyl and (C<sub>1</sub>-C<sub>8</sub>)-alkoxy representing R<sup>10</sup> are unsubstituted or substituted by at least one identical or different substituent chosen from (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl-, hydroxycarbonyl- and aminocarbonyl-,

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wherein each of the aryl groups and Het group in a group R<sup>10</sup> is unsubstituted or substituted by at least one identical or different substituent chosen from halogen, nitro, oxo, hydroxy, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>1</sub>-C<sub>8</sub>)-alkoxy, (C<sub>1</sub>-C<sub>4</sub>)-alkoxy-(C<sub>2</sub>-C<sub>4</sub>)-alkoxy-, (C<sub>6</sub>-C<sub>14</sub>)-aryloxy-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkoxy-, Het-oxy-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkoxy-, (C<sub>6</sub>-C<sub>14</sub>)-aryl, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, Het, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-, trifluoromethyl, cyano, trifluoromethoxy, (C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl-, hydroxycarbonyl-, aminocarbonyl-, amino, (C<sub>1</sub>-C<sub>8</sub>)-alkylamino-, di-((C<sub>1</sub>-C<sub>8</sub>)-alkyl)amino-, (C<sub>1</sub>-C<sub>8</sub>)-alkylcarbonylamino-, (C<sub>6</sub>-C<sub>14</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylcarbonylamino-, (C<sub>6</sub>-C<sub>14</sub>)-arylcarbonylamino-, Het-carbonylamino-, Het-(C<sub>1</sub>-C<sub>4</sub>)-alkylcarbonylamino-, and (C<sub>1</sub>-C<sub>8</sub>)-alkylcarbonyl-, wherein (C<sub>1</sub>-C<sub>8</sub>)-alkyl and (C<sub>1</sub>-C<sub>8</sub>)-alkoxy representing a substituent on an aryl group or Het group in a group R<sup>10</sup> are unsubstituted or substituted by at least one identical or different substituent chosen from (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl-, hydroxycarbonyl- and aminocarbonyl-.

with the proviso that, when a substituent R<sup>10</sup> is bonded to an alkyl group, it cannot be (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl-, hydroxycarbonyl-, aminocarbonyl-, (C<sub>1</sub>-C<sub>8</sub>)-alkylaminocarbonyl-, or (C<sub>1</sub>-C<sub>8</sub>)-alkylaminosulfonyl-, and that, when a substituent R<sup>10</sup> is bonded to an alkyl group, it cannot be (C<sub>1</sub>-C<sub>8</sub>)-alkyl which is substituted by at least one identical or different substituent

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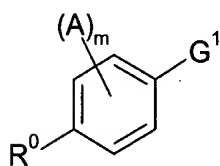
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chosen from (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl-, hydroxycarbonyl- and aminocarbonyl-;

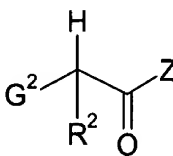
Het is a residue of a saturated or unsaturated monocyclic or bicyclic, 3-membered to 10-membered heterocyclic ring system containing 1, 2 or 3 identical or different ring heteroatoms chosen from nitrogen, oxygen and sulfur;

or a physiologically tolerable salt thereof, in any stereoisomeric form, or a mixture of any such compounds in any ratio.

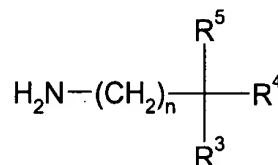
7. (AMENDED) A process for the preparation of at least one compound of formula I as claimed in claim 1, comprising linking the compounds of formulae II, III and IV with formation of a (thio)urea bridge between the groups [G<sup>1</sup> and G<sup>2</sup>] G<sup>1</sup> and G<sup>2</sup> in formulae II and III and an amide bond between the COZ group in formula II and the NH<sub>2</sub> group in formula IV,



II.



III



IV

wherein

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- (a)  $G^1$  is  $NH_2$  and  $G^2$  is chosen from iso(thio)cyanato,  $(C_1-C_6)$ -alkoxycarbonylamino, trichloromethylcarbonylamino, and azolyl-N-(thio)carbonylamino, wherein these groups contain the group  $R^6$ ; or
- (b)  $G^1$  is chosen from iso(thio)cyanato,  $(C_1-C_6)$ -alkoxycarbonylamino, trichloromethylcarbonylamino, and azolyl-N-(thio)carbonylamino and  $G^2$  is  $NHR^6$ ; and

Z in the compound of formula III is chosen from hydroxy and a nucleophilically substitutable leaving group;  $R^0$  in the compound of formula II is chosen from  $R^1NH-C(=NH)-$ , a protected form thereof, and a precursor group thereof; and m, n, A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are defined as in claim 1, but wherein functional groups can also be present in protected form or in the form of precursor groups.

11. (AMENDED) A method of inhibiting or reducing blood clotting or inflammatory response, [or treating cardiovascular disorders, thromboembolic diseases or restenoses,] comprising administering to a patient an effective amount of at least one compound chosen from the compounds of the formula I as claimed in claim 1 and their physiologically tolerable salts.

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